Cortical blood flow in controlled hypotension as measured by thermal diffusion

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SUMMARY A thermal diffusion flow probe which gave a continuous, dynamic, quantitative record of cortical blood flow (CBF) was used to assess CBF in experimental animals with controlled hypotension. Acute hypotension was produced by trimethaphan camsylate, halothane, and sodium nitroprusside. Halothane produced less reduction in CBF per drop in blood pressure than the other two agents.

Controlled hypotension has been a valuable operative adjunct for the neurosurgeon since 1946 when Gardner first used arteriotomy to facilitate removal of a large olfactory groove meningioma. In 1953 Wiklund recommended pharmacologically controlled hypotension for aneurysms, vascular tumours, arteriovenous malformations, and increased intracranial pressure with cerebral oedema. As experience with the technique accumulated, the primary indication has become the direct approach to intracranial aneurysms. Three modes of hypotension are currently used: trimethaphan camsylate (Arfonad), deep halothane anaesthesia, and sodium nitroprusside. This study was designed to evaluate the effects of these three agents on cortical blood flow (CBF) because of the ever-present spectre of cerebral ischaemia with controlled hypotension.

Cerebral blood flow may be measured by numerous methods including Kety-Schmidt’s (1945) nitrous oxide diffusion washout, electromagnetic flowmeters on large vessels, venous outflow collection, radioactive gas diffusion washout (Lassen and Ingvar, 1961), and autoradiography (Landau, Freygang, Roland, Sokoloff, and Kety 1955). Since a dynamic continuous record of tissue perfusion was desired, a thermal diffusion probe as described by Brawley (1968) was investigated.

Gibbs first measured blood flow with a thermal diffusion device in 1933, and in more recent years Grayson (1952) was able to show a linear relationship between blood flow and the heat conductivity increment in tissue. Betz and Willenwebner (1962), Betz, Ingvar, Lassen, and Schmahl (1966), Betz and Heuser (1967), Betz (1968), using a technique described by Hensel (1959), have made extensive measurements of cerebral cortical blood flow. Their probe had two small gold plates, one heated and one neutral, which were placed on the cortex. Temperature difference between the two plates was found to be related to CBF to a depth of 1.5 mm. Betz et al. (1966) pointed out that their results were affected by local vascular geometry, which might account for their lack of correlation of CBF as measured by $^{85}$Kr clearance and thermal diffusion between animals of the same species. Brawley (1968) used a Peltier stack to create a probe with one heated and one cooled plate. This probe utilized the Peltier thermoelectric effect to produce a thermal gradient by current flow through a semiconductor. The temperature gradient was conducted to the tissue by two metal plates which were thermally contiguous with the respective hot and cold sides of the semiconductor stack, but electrically isolated.

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from its current. The difference in temperature between the two plates varied with CBF. Ideally ambient temperature variations would not affect the recorded temperature differences.

**METHODS**

Our probe is a modification of Brawley’s (Fig. 1). An 'L'-shaped gold plate was soldered to each surface of the Peltier device and copper-constantine thermocouples were spot welded to the approximate centre of the back of the cerebral contact surface and were connected with opposite polarity so that the output of the pair was zero when at the same temperature. Temperature differences of the thermocouples produced an output of the order of hundreds of microvolts which was recorded on a Grass model 7 polygraph. A small steel rod was used for fixation of the probe to the head holder, and the probe, with the exception of the cerebral contact surfaces, was encased in epoxy resin.

The contact plates each measured 0.50 cm x 0.75 cm. Three hundred mA direct current through the Peltier stack produced the temperature gradient at the plates of 5°C above and 3°C below the cortical temperature. The temperature differences varied with cortical blood flow. *In vitro* tests of the probe revealed that, despite a gradual drop in surface temperature from 35.25° to 26.00°C, no significant changes in temperature gradient between the two plates occurred, thus demonstrating its independence of cortical ambient temperature. The time constant of the probe was found to be 4.2 sec.

Twelve mongrel cats anaesthetized with intraperitoneal pentobarbitone (35 mg/kg), except one which was induced and maintained on inhaled halothane alone, had Teflon cannulae inserted into both femoral artery and femoral vein and tracheostomy performed. The arterial cannula was connected to a Statham strain gauge for recording blood pressure, and the venous cannula was used for injection of drugs. Additional intravenous pentobarbitone was used to keep the animal well sedated throughout surgery, and a small left craniectomy was performed. Great care was taken to obtain good haemostasis before the dura mater was opened. Fifty millilitres D5W and 7 to 9 mEq NaHCO₃ were given intravenously during the surgery to correct any slight ketosis that may have been present because the cats were fasting the night before surgery. The animals were then placed on a positive pressure respirator breathing room air with supplemental O₂ and paralysed with gallamine triethiodide (5 mg/kg). After at least 30 minutes for stabilization, arterial blood gases were drawn and, if necessary, adjustments in volume and rate of respiration were made followed by repeat estimation of blood gases. Blood pressure (BP) and respiration were monitored by strain gauges. To record, the probe was lowered onto the crown of a gyrus, attempting to avoid large surface vessels. Enough pressure was applied to hold contact with the cortex without causing any signifi-
significant deformity. The plates and surrounding cortex were covered. Connecting the two contact plates together electrically revealed no significant changes in gradient as measured by the thermocouples, indicating the absence of a significant bioelectric potential between the two plates. To evaluate the approximate sensitivity of the probe, layers of moist cottonoids were placed between the probe and cortex. Changes in blood flow could be detected readily through 3 mm of cottonoid but were markedly attenuated.

Calibration of the Peltier flow probe was carried out by correlation with $^{133}$Xe diffusion-washout curves in the cat. In four of the animals large right craniectomies were performed. After the dura mater was opened, the cortex was covered with polyvinyl chloride film. A 1.25 in. thin mica end window Geiger–Muller tube with output fed to a ratemeter and then to the polygraph was placed as near the right cortex as possible. One microcurie of $^{133}$Xe dissolved in 0.1 ml saline followed by a 0.3 ml flush of saline at 37°C was injected rapidly into the brachiocephalic artery through a Teflon catheter in the right subclavian artery. The blood flow probe on the left hemisphere was monitored while obtaining $^{133}$Xe diffusion-washout curves on another channel in order to ensure uniformity of CBF.

It was felt that the washout curves from the exposed cortex of the cat would give the most accurate assessment of CBF, since it is extremely difficult to separate the extracranial from the cerebral circulation in this animal. Harper and Jennett (1968) have shown that the beta curve, presumably strictly cortical flow, and the fast component of the gamma curve correlate quite well. Only the fast component was considered, since we were concerned only with cortical flow. The CBF was altered by changing the $P_{CO_2}$, as well as a slow phenylephrine intravenous drip which increased CBF and blood pressure. All curves with a peak of less than 9,000 counts per minute and in which the Peltier flow channel did not show a constant flow throughout the diffusion curve were discarded.

The half time ($t_{1/2}$) in minutes for $^{133}$Xe diffusion from grey matter was found, and, using principles advocated by Lassen and Ingvar (1961) with Hoedt–Rasmussen’s (1967) correction for Hb, the CBF in ml./100 g/min was calculated.

$$\text{CBF in ml./100 g/min} = \frac{100 \times 0.693}{t_{1/2}} \lambda$$

$\lambda$ is the brain blood partition coefficient for $^{133}$Xe.

A dead brain thermal value for the flow probe was found at the end of the experiment after cardiac arrest caused by intravenous injection of KCl.
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(Fig. 2). The probe output voltage for each $^{133}$Xe determination was found and subtracted from the dead brain value. Fourteen values of CBF as determined by the flow probe and $^{133}$Xe washout curves were obtained.

In the second phase of the experiment three methods of producing hypotension acutely were utilized: (1) trimethaphan camsylate (Arfonad) 10 mg/100 ml. D5W intravenous drip, (2) deep halothane anaesthesia which was controlled by a halothane analyser-vaporizer-controller$^4$, and (3) sodium nitroprusside 2 mg/100 ml. D5W intravenous drip. Halothane concentrations were varied from 1 to 4%. Two percent halothane was found to produce rapid hypotension. Blood pressure (BP) was lowered in 1-5 to 10 minutes using several different agents in the same cat as well as the repeated use of the same

4 Courtesy of Ohio Medical Products.

agent in the same cat. The results of normalized CBF changes per drop in BP were correlated with the Digital PDP-12 computer.

**RESULTS**

A linear relationship was noted between CBF as measured by $^{133}$Xe diffusion washout and the flow probe. When plotted in a least squares manner on the Digital PDP-12 computer the relationship was found to be:

$$\text{CBF probe} \text{ in ml./100 g/min } = 2.18 \times ^{133}\text{Xe} - 8.58$$

Root mean squared (RMS) error $= 11.7 \mu V$

(see Fig. 3)

Data reduction in the pharmacologically controlled hypotension experiments began with the elimination of all data from animals which had suffered haemorrhage, cortical contusion, hypercarbia, or hypoxia, since damage to the cerebrovascular regulatory system may have occurred. This same regulatory system would be lost outside the autoregulatory range of BP, therefore any data with a minimum mean BP below 70 mmHg were discarded. CBF autoregulation has been demonstrated by Haggendal and Johansson (1966) to occur under normo- and hypocapnic conditions in ranges of pH from 7-26 to 7-87. Final constraints for control values were then defined as $P_{CO_2}$ from 24-5 to 40-5 mmHg, pH from 7-26 to 7-45 and CBF above 24 ml./100 g/min. Twenty five observations in eight animals met the above criteria.

Control CBF was below normal values for awake animals but in an acceptable range for animals under barbiturate anaesthesia and was an average of 48.1, 61.9, and 56.1 ml./100 g/min for the trimethaphan camsylate, sodium nitroprusside, and halothane groups respectively. The one animal that did not receive a barbiturate maintained a higher CBF than the other animals.

Because of the difference in techniques of administration of the agents, the time to reduce the BP was quite variable. The average time to produce maximum hypotension in the trimethaphan camsylate, sodium nitroprusside, and halothane groups was 3.7 min, 3.1 min, and 5.2 min respectively. No attempt was made to maintain hypotension and once hypotension was achieved the agent was discontinued and the
Trimethaphan camsylate 7 33.6 ± 2.4† 140.9 ± 3.3 48.1 ± 7.1 32.0 ± 2.5 40.1 ± 7.1 1.227 ± 0.229
Sodium nitroprusside 9 33.8 ± 2.4 142.3 ± 5.3 61.9 ± 7.6 24.9 ± 2.6 23.6 ± 4.4 0.908 ± 0.112
Halothane 9 31.8 ± 2.4 133.0 ± 3.8 56.1 ± 11.2 22.6 ± 2.5 8.7 ± 2.6 0.365 ± 0.120

* ΔBP% and ΔCBF% are the percent changes in BP and CBF.
† Standard error of mean.

TABLE 2
STATISTICAL EVALUATION OF THE THREE HYPOTENSIVE AGENTS*

<table>
<thead>
<tr>
<th>Agents</th>
<th>ΔPCO2 (mmHg)</th>
<th>ΔControl BP (mmHg)</th>
<th>ΔControl CBF (ml/100 g/min)</th>
<th>ΔCBF%</th>
<th>ΔACBF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethaphan camsylate and nitroprusside</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Trimethaphan camsylate and halothane</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Significant at 0.05 not at 0.01</td>
</tr>
<tr>
<td>Nitroprusside and halothane</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>Significant at 0.01</td>
</tr>
</tbody>
</table>

* BP was lowered more with trimethaphan camsylate; however, taking this into consideration by using the ratio of ΔCBF%/ΔBP%, halothane had significantly less effect on CBF.
† NS = not significant.

BP was allowed to return to control levels. In general, the hypotension produced by trimethaphan camsylate persisted longer than hypotension produced by the other two agents.

CBF autoregulation is best demonstrated by gradual hypotension (Bozzao, Fieschi, Agnoli, and Nardini, 1968), and, since the rate of change in these experiments is rapid, it is not possible to assess the impact of these agents on the autoregulation mechanism. We did note that the minimum CBF usually occurred simultaneously with maximum hypotension and the CBF gradually returned to normal concomitantly with BP.

The three groups were quite comparable, with no statistical differences regarding control mean BP, CBF, and PCO2, and met the criteria for a homogeneous population in an autoregulation design. The minimum CBF during controlled hypotension was compared with the control CBF in each individual run regarding percent change in CBF per percent change in mean BP. Trimethaphan camsylate depressed CBF per drop in BP the most, followed by sodium nitroprusside, while halothane had significantly less effect on CBF for the same change in BP (Tables, 1, 2).

The CBF as recorded by the flow probe was linearly related to the cortical flow as determined by 133Xe diffusion-washout curves. Cortical blood flow decreased with all three hypotensive agents; however, the percent drop of CBF per percent drop of BP was significantly less with halothane than with the other two agents.

DISCUSSION

The linear correlation of thermal diffusion measured CBF with radioactive diffusion-washout measured CBF was demonstrated up to 90 ml./100 g/min and may persist at higher rates of flow. This correlation is at variance with the results of Betz et al. (1966, 1967, 1968) which demonstrated a reproducible relationship of CBF as measured by heat clearance and by 85Kr washout in the same animal, with variations between animals. It must be kept in mind that their probe differed from the one used in this
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...experiment in two important respects: (1) the size of the cortical contact surface, and (2) the temperature of the non-heated plate. Both of these factors make their probe dependent on the local vascular geometry as pointed out by Betz et al. (1966). On the other hand, the probe used in this experiment has a larger cortical contact surface area, thus producing an averaging effect, and the non-heated surface is actively cooled, therefore minimizing the thermal effect produced on it by the heated plate.

The Peltier flow probe is able to record continuous changes in CBF in a quantitative manner with reproducible results from one experiment to the next, and acute changes are noted without difficulty within the limits of the time constant. The prime disadvantage of the probe is the need to expose the cortex; however, under the conditions of interest—that is, intracranial surgery—the cortex is exposed. Since the thermal diffusion properties of cortical tissue are relatively constant the probe provides the means to measure simply regional CBF quantitatively in the surgical theatre as has been done qualitatively by Betz and Wullenweber (1962).

Other popular methods of measuring CBF all have some disadvantages when applied to this particular experimental problem as well as in the operating room. The nitrous oxide and radioactive diffusion-washout technique require a constant blood flow for a period of time and are unable to demonstrate CBF dynamics. Venous outflow measuring systems usually require extensive surgery and cannot differentiate arteriovenous shunting from actual tissue perfusion. Examination of pial circulation will give crude qualitative estimates of flow, but, because the flow is proportional to the fourth power of the radius of the vessel, minute changes in the radius can alter the flow.

The well-known autoregulatory mechanism of CBF in systemic hypotension has been well documented with gradual changes in blood pressure produced by hemorrhage (Harper 1966). Due to the nature of most CBF measuring systems very little information is available concerning acute pharmacological reduction in BP as occurs in surgically controlled hypotension.

Because of the variations in the character and modes of administration of these agents it is...

(a) Intravenous infusion of trimethaphan camsylate given between the two downward deflections of the event marker. BP (mmHg) and CBF (ml/100 gm/min) both dropped rapidly.

(b) Intravenous sodium nitroprusside infused between the two downward deflections of the event marker, demonstrating again a concomitant fall in BP and CBF. CBF did not drop as much as with trimethaphan camsylate, and return to previous flow rate occurred much more promptly.

(c) Hypotension produced by 2% halothane inhalation. Halothane concentration is recorded on the polygraph tracing. No effect in CBF was noted during the drop in BP. Upward deflection of time marker is at five second intervals.

atm = atmospheric pressure.

FIG. 4. Three separate tracings demonstrating the effect of the three agents in the same animal.
difficult to compare them. In this experimental setting the hypotension produced by halothane was not as rapid and the hypotension produced by trimethaphan camsylate seemed more persistent. Since the speed with which hypotension is produced may be a factor in preservation of autoregulation (Bozzao et al., 1968), the more gradual hypotension of halothane may have contributed to the better preservation of CBF with this agent.

Trimethaphan camsylate acts as a ganglionic blocking agent and has been used extensively for controlled surgical hypotension for many years. Moyer and Morris (1954) demonstrated a decrease in CBF in the awake normotensive patient with trimethaphan camsylate as well as with other ganglionic blocking agents. They found a 32% fall in nitrous oxide measured CBF with a 42% fall in mean BP. During hypotension the calculated \( \frac{\Delta \text{CBF}}{\Delta \text{BP}} \% \) is 0.762 as compared with 1.227 for our anaesthetized paralysed cats. The fall in CBF, while not as great as in our experimental animals, was significant and did demonstrate that even in awake normal volunteers trimethaphan camysylate will markedly decrease CBF.

Sodium nitroprusside has been studied by Moraca, Bitte, Hale, Wasmuth, and Poutasse (1962) and found to be an excellent agent for controlled surgical hypotension because of the prompt appearance and disappearance of its effects. It is thought to act directly on the vascular musculature rather than on the nervous control. Very little information is available on its effect on CBF. Waltz (1968) used several agents including sodium nitroprusside to reduce BP in cats and found no decrease in CBF in nonischaemic cortex. Cortical blood flow was measured with radioactive clearance washout curves, and no details of the temporal relationship of the agent and recording CBF were given.

McDowall (1967) found that halothane increased CBF in concentrations not sufficient to produce hypotension, and barbiturates are known to depress CBF (Landau et al., 1955). In a concentration of 2%, halothane rapidly reduced the mean BP as well as the pulse pressure. In most cases, the flow did not drop as markedly as with the other agents. Comparison of an animal that received all three agents is seen in Fig. 4. It is obvious that the effect of halothane on CBF was not as marked as was that of the other two.

Using \(^{85}\text{Kr}\) and \(^{133}\text{Xe}\), Christensen, Høedt-Rasmussen, and Lassen (1965) measured CBF in four patients before and during halothane anaesthesia. They found a \( \frac{\Delta \text{CBF}}{\Delta \text{BP}} \% \) of 0.457 which is comparable with the 0.365 ratio for our animals. In controlled hypotension halothane has a less depressant effect on CBF than sodium nitroprusside and trimethaphan camsylate.

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